Integrin β3 knockdown suppresses TGF-β2-induced migration and epithelial–mesenchymal transition in human lens epithelial cells

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Conflict of interest
None declared

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Abstract

Background. Posterior capsular opacification (PCO) is a common complication of cataract surgery and is strongly associated with the epithelial–mesenchymal transition (EMT) of lens epithelial cells (LECs). Integrin β3 (*ITGB3*) has been implicated in various pathological processes; however, its role in PCO remains insufficiently understood.

Objectives. To investigate the regulatory role of *ITGB3* in PCO progression and determine whether *ITGB3* modulates transforming growth factor-β2 (TGF-β2)-induced migration and EMT in human lens epithelial cells.

Materials and methods. Human lens epithelial HLE-B3 cells were treated with transforming growth factor-β2 (TGF-β2; 10 ng/mL) to establish an in vitro model of PCO. *ITGB3* expression at the mRNA and protein levels was assessed using reverse transcription quantitative polymerase chain reaction (RT-qPCR) and western blotting. Cell proliferation was evaluated using the 5-ethynyl-2′-deoxyuridine (EdU) assay, while cell migration was assessed using transwell and wound-healing assays.

Results. TGF-β2 stimulation significantly increased *ITGB3* expression in HLE-B3 cells. Silencing of *ITGB3* significantly reduced the proliferation of TGF-β2-treated cells and inhibited their migratory capacity, as demonstrated by both transwell and wound-healing assays. Exposure to TGF-β2 promoted EMT, whereas ITGB3 knockdown reversed this effect. Furthermore, activation of the TGF-β/Smad2/3 signaling pathway induced by TGF-β2 was attenuated following *ITGB3* silencing.

Conclusions. Knockdown of *ITGB3* alleviates TGF-β2-induced migration and EMT in HLE-B3 cells by suppressing the TGF-β/Smad2/3 signaling pathway, supporting *ITGB3* as a potential therapeutic target for the prevention and treatment of PCO.

Key words: integrin beta 3, transforming growth factor beta 2, epithelial–mesenchymal transition, lens epithelial cells, posterior capsular opacification

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Highlights

- *ITGB3* was highly expressed in HLE-B3 cells stimulated by transforming growth factor (TGF)-β2.
- Inhibition of *ITGB3* reduced the proliferation of HLE-B3 cells exposed to TGF-β2.
- Knockdown of *ITGB3* suppressed cell migration.
- Silencing *ITGB3* attenuated the epithelial–mesenchymal transition (EMT) process and weakened activation of the TGF-β/Smad2/3 pathway.

Background

Posterior capsular opacification (PCO) is one of the most common complications following cataract surgery and remains a leading cause of visual impairment and secondary blindness in affected patients.[1] Following cataract extraction, wound-healing responses are activated within the eye, inducing the proliferation, migration, and epithelial–mesenchymal transition (EMT) of residual lens epithelial cells (LECs), thereby contributing to the development of PCO.[2] At present, no drugs or molecular targets are available that can be safely and effectively applied in clinical practice for the treatment or prevention of PCO. Therefore, identifying novel therapeutic targets to prevent or ameliorate PCO has become an important research priority.[3]

Integrins are heterodimeric adhesion receptors that physically link cells to the extracellular matrix (ECM) and play essential roles not only in cellular anchorage but also in intracellular signaling.[4] Through these combined functions, integrins influence numerous physiological and pathological processes.[5] Among them, integrin β3 (*ITGB3*) has been shown to exert important regulatory effects in a variety of diseases. For example, platelet-derived extracellular vesicles upregulate *ITGB3* expression, promote distant metastasis of nasopharyngeal carcinoma, and inhibit ferroptosis.[6] In osteosarcoma, *ITGB3* activation influences the MAPK and VEGF signaling pathways, enhancing cisplatin resistance and contributing to disease progression.[7] Furthermore, miR-25-3p regulates *ITGB3* in osteoporosis and suppresses the osteogenic differentiation of bone marrow stromal cells (BMSCs).[8] The *ITGB3*–PKM2 axis has also been implicated in alleviating aerobic glycolysis and exerting protective effects against mechanical ventilation-induced pulmonary fibrosis.[9] In addition, downregulation of *ITGB3* by isoliquiritigenin has been reported to reduce renal fibrosis and protect against tubular cell senescence.[10] Importantly, *ITGB3* has also been associated with enhanced transforming growth factor-beta (TGF-β) secretion, a key driver of EMT.[10,11] Despite these findings, the regulatory role of *ITGB3* and its associated signaling pathways in the progression of PCO remains poorly understood.

Objectives

This study was designed to investigate the regulatory role of *ITGB3* in PCO progression and to elucidate the involvement of its associated signaling pathways, with the aim of identifying potential molecular targets for the prevention and treatment of PCO.

Materials and methods

Cell lines and treatment

Human lens epithelial B3 cells (HLE-B3; AC340494) were purchased from the American Type Culture Collection (ATCC; Manassas, USA). The cells were cultured in Dulbecco's modified Eagle's medium (DMEM; Gibco, Waltham, USA) supplemented with 10% fetal bovine serum (FBS; Gibco) and maintained at 37°C in a humidified incubator containing 5% CO_2. To establish an in vitro model of PCO, HLE-B3 cells were treated with transforming growth factor-β2 (TGF-β2; 10 ng/mL; Cell Signaling Technology (CST), Danvers, USA) for 48 h.

Cell transfection

For gene silencing, HLE-B3 cells were transfected with small interfering RNAs targeting *ITGB3* (si-ITGB3; sequence: GAAAAUCCGUUCUAAAGUA) or a negative control siRNA (si-NC; GenePharma, Shanghai, China) using Lipofectamine 2000 (Invitrogen, Waltham, USA). Transfection was performed according to the manufacturer's instructions, and the cells were incubated for 48 h before subsequent experiments.

RT-qPCR

Total RNA was extracted from HLE-B3 cells using TRIzol reagent (Invitrogen). Complementary DNA (cDNA) was synthesized using the PrimeScript™ RT Master Mix Kit (Takara, Dalian, China), and reverse transcription quantitative polymerase chain reaction (RT-qPCR) was performed using the SYBR Premix Ex Taq™ Kit (Takara).

Gene expression was analyzed using the $2^{-\Delta\Delta Ct}$ method, with *GAPDH* serving as the internal control.

The primer sequences were as follows:

ITGB3

Forward: 5′-CCAGCACCATCTCTTTAC-3′;
Reverse: 5′-CTTATTCCCAGCCAACTC-3′.

GAPDH

Forward: 5′-CCTCTTGACTTCAACAGCGACCAC-3′;
Reverse: 5′-TGGTCCAGGGGTCTTACTCC-3′.

Western blotting

Total protein was extracted from HLE-B3 cells using radioimmunoprecipitation assay (RIPA) lysis buffer. Equal amounts of protein were separated using 10% sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS–PAGE) and subsequently transferred onto polyvinylidene fluoride (PVDF) membranes (Beyotime, Shanghai, China). After blocking, the membranes were incubated overnight at 4°C with the following primary antibodies: ITGB3 (ab179473; rabbit monoclonal; 1:1,000), Smad3 (ab40854; rabbit monoclonal; 1:1,000), phospho-Smad3 (ab63403; rabbit polyclonal; 1:500), Smad2 (ab40855; rabbit monoclonal; 1:2,000), phospho-Smad2 (ab280888; rabbit monoclonal; 1:1,000), alpha-smooth muscle actin (α-SMA; ab5831; mouse monoclonal; 1:1,000), vimentin (ab92547; rabbit monoclonal; 1:1,000), E-cadherin (ab40772; rabbit monoclonal; 1:1,000), N-cadherin (ab76011; rabbit monoclonal; 1:5,000), and β-actin (ab9485; mouse monoclonal; 1:1,000) (all from Abcam, Shanghai, China). The membranes were then incubated for 2 h at room temperature with horseradish peroxidase (HPA)-conjugated secondary antibodies (ab7090; goat anti-rabbit; 1:2,000; Abcam). Protein bands were visualized using an enhanced chemiluminescence detection kit (Thermo Fisher Scientific, Waltham, USA) and quantified using ImageJ v. 2.2.0 (National Institutes of Health (NIH), Bethesda, USA).

5-ethynyl-2′-deoxyuridine cell proliferation assay

Cell proliferation was evaluated using the 5-ethynyl-2′-deoxyuridine (EdU) assay (50 μM; RiboBio, Guangzhou, China). HLE-B3 cells were incubated with EdU for 2 h, fixed with 4% paraformaldehyde, and permeabilized using 0.5% Triton X-100. The cells were then stained with Apollo dye solution and counterstained with DAPI (4′,6-diamidino-2-phenylindole). EdU-positive cells were visualized under a fluorescence microscope Leica DM2500; Leica Microsystems, Wetzlar, Germany). The percentage of proliferating cells was calculated using the following formula:

$$\text{EdU-positive cells (\%)} = (\text{EdU-positive cells/DAPI-positive cells}) \times 100\%$$

Transwell migration assay

Cell migration was assessed using Transwell chambers (Corning Life Sciences, Corning, USA). A suspension of HLE-B3 cells (1×10^5 cells in 200 μL of DMEM) was seeded into the upper chamber, while the lower chamber was filled with 600 μL of medium containing 20% FBS as a chemoattractant. After 24 h, migrated cells on the lower surface of the membrane were fixed with 90% ethanol, stained with 0.1% crystal violet, and counted in 5 randomly selected fields under a light microscope (IX73; Olympus Corp., Tokyo, Japan).

Wound healing assay

HLE-B3 cells (1×10^5 cells) were seeded into 6-well plates and grown to confluence. A linear scratch was created across the cell monolayer using a sterile pipette tip, and cell migration into the wound area was observed at 0 h and 24 h. Images were captured using a light microscope (IX73; Olympus Corp.), and wound closure was quantified using ImageJ software.

Statistical analyses

Each experimental group consisted of 3 independently treated biological replicates. The expression of collagen 1A1, fibronectin, vimentin, and cell migration in human lens epithelial cells (HLECs) showed a normal distribution when n = 3, and comparisons among multiple groups or between 2 groups were conducted using one-way analysis of variance (ANOVA) or Student's t-test.[12] Protein expression, autophagy, and EMT-related experiments also showed a normal distribution when the experiments were repeated 3 times.[13] Comparisons between 2 groups were analyzed using Student's t-test, whereas comparisons among multiple groups were analyzed using ANOVA. Therefore, according to the statistical guidelines by Kujawa et al.,[14] data in this study are presented as the mean ± standard deviation (SD). Comparisons between 2 groups were performed using an unpaired Student's t-test, while comparisons among multiple groups were performed using one-way ANOVA followed by Tukey's post hoc test. Statistical analyses and graphical presentations were generated using GraphPad Prism v. 9.0 (GraphPad Software, San Diego, USA), and $p < 0.050$ was considered statistically significant.

Results

ITGB3 expression is upregulated in HLE-B3 cells following TGF-β2 stimulation

Reverse transcription-quantitative polymerase chain reaction analysis revealed that *ITGB3* mRNA expression was significantly increased following transforming growth

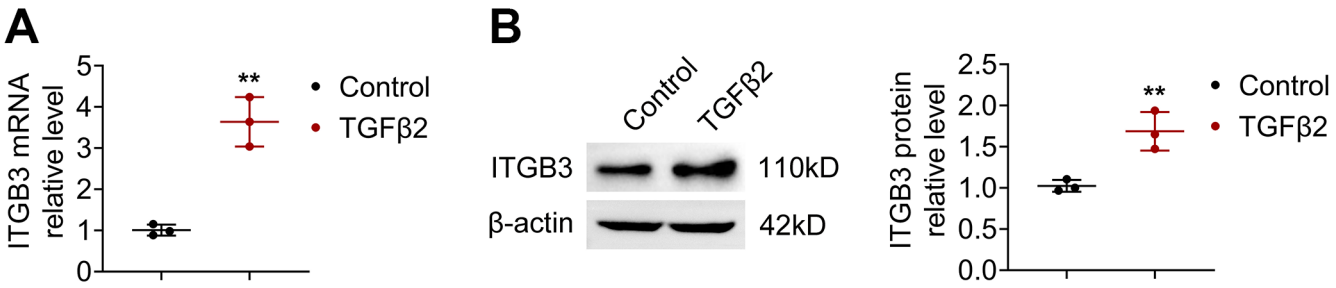

Fig. 1. *ITGB3* expression is upregulated in HLE-B3 cells after transforming growth factor (TGF)-β2 stimulation. A. *ITGB3* mRNA expression in the control and TGF-β2-treated groups was measured using reverse transcription quantitative polymerase chain reaction (RT-qPCR); B. *ITGB3* protein expression in the control and TGF-β2-treated groups was analyzed using western blotting (n = 3, **p < 0.01)

factor (TGF)-β2 treatment (Fig. 1A). Consistently, western blotting demonstrated elevated ITGB3 protein levels in HLE-B3 cells exposed to TGF-β2 (Fig. 1B). These findings confirm that TGF-β2 stimulation induces increased *ITGB3* expression at both the mRNA and protein levels in HLE-B3 cells.

Inhibition of *ITGB3* attenuates TGF-β2-induced proliferation of HLE-B3 cells

The transfection efficiency of si-*ITGB3* was verified (Fig. 2A), and TGFβRII protein expression remained unchanged across all groups, indicating the specificity of the knockdown. ITGB3 protein expression, which was elevated following TGF-β2 stimulation, was markedly reduced after si-*ITGB3* transfection (Fig. 2B). Functionally, TGF-β2 enhanced the proliferation of HLE-B3 cells; however, this effect was significantly attenuated following *ITGB3* inhibition (Fig. 2C). Collectively, these results suggest that *ITGB3* silencing suppresses TGF-β2-induced proliferation in HLE-B3 cells.

Knockdown of *ITGB3* suppresses cell migration

The transwell assay showed that TGF-β2 stimulation significantly increased the migration of HLE-B3 cells, whereas *ITGB3* knockdown counteracted this effect (Fig. 3A,B). A similar trend was observed in the wound-healing assay, in which the enhanced migratory capacity induced by TGF-β2 was reversed following *ITGB3* silencing (Fig. 3C,D). These results demonstrate that *ITGB3* knockdown effectively restrains TGF-β2-induced migration of HLE-B3 cells.

Suppression of *ITGB3* attenuates EMT progression

Western blotting demonstrated that TGF-β2 stimulation reduced E-cadherin expression and increased N-cadherin expression, consistent with the induction of EMT. These changes were reversed following *ITGB3* suppression (Fig. 4A). Moreover, the protein levels of α-SMA and vimentin, both markers of EMT, were elevated by TGF-β2 but decreased following *ITGB3* knockdown (Fig. 4B). Together, these findings indicate that *ITGB3* silencing attenuates EMT progression in HLE-B3 cells.

ITGB3 knockdown inhibits activation of the TGF-β/Smad2/3 pathway

TGF-β2 treatment enhanced the phosphorylation of Smad2 and Smad3, as indicated by increased p-Smad2/Smad2 and p-Smad3/Smad3 ratios. Silencing *ITGB3* significantly reduced these phosphorylation events (Fig. 5). Overall, these results indicate that *ITGB3* knockdown may impair activation of the TGF-β/Smad2/3 signaling pathway in TGF-β2-treated HLE-B3 cells.

Discussion

The development of PCO is a complex process involving multiple cytokines.[15] Among these, TGF-β has been identified as one of the most potent cytokines driving the trans-differentiation and fibrosis of LECs.[16] TGF-β promotes the proliferation, migration, and EMT of LECs; therefore, TGF-β2-treated LECs are widely used as an in vitro model for PCO research.[17,18] In the present study, this model was established by stimulating HLE-B3 cells with TGF-β2 at a concentration of 10 ng/mL.

ITGB3 has been shown to exert important regulatory functions in various pathological contexts.[6–10] However, its role in PCO progression remains unclear. Our results demonstrated that *ITGB3* expression was significantly upregulated in HLE-B3 cells following TGF-β2 treatment. Furthermore, inhibition of *ITGB3* reduced the proliferative response of these cells, suggesting that *ITGB3* may contribute to TGF-β2-induced cell proliferation.

Both cell migration and EMT are central to the progression of PCO. Considerable attention has been directed toward identifying the molecular mechanisms that regulate these processes. For instance, miR-30a targets Smad2 to attenuate EMT and cell migration in PCO,[19] TP53INP2 enhances autophagy to accelerate EMT and migration,[13] and REPS2 regulates FAK/Cdc42 signaling to modulate

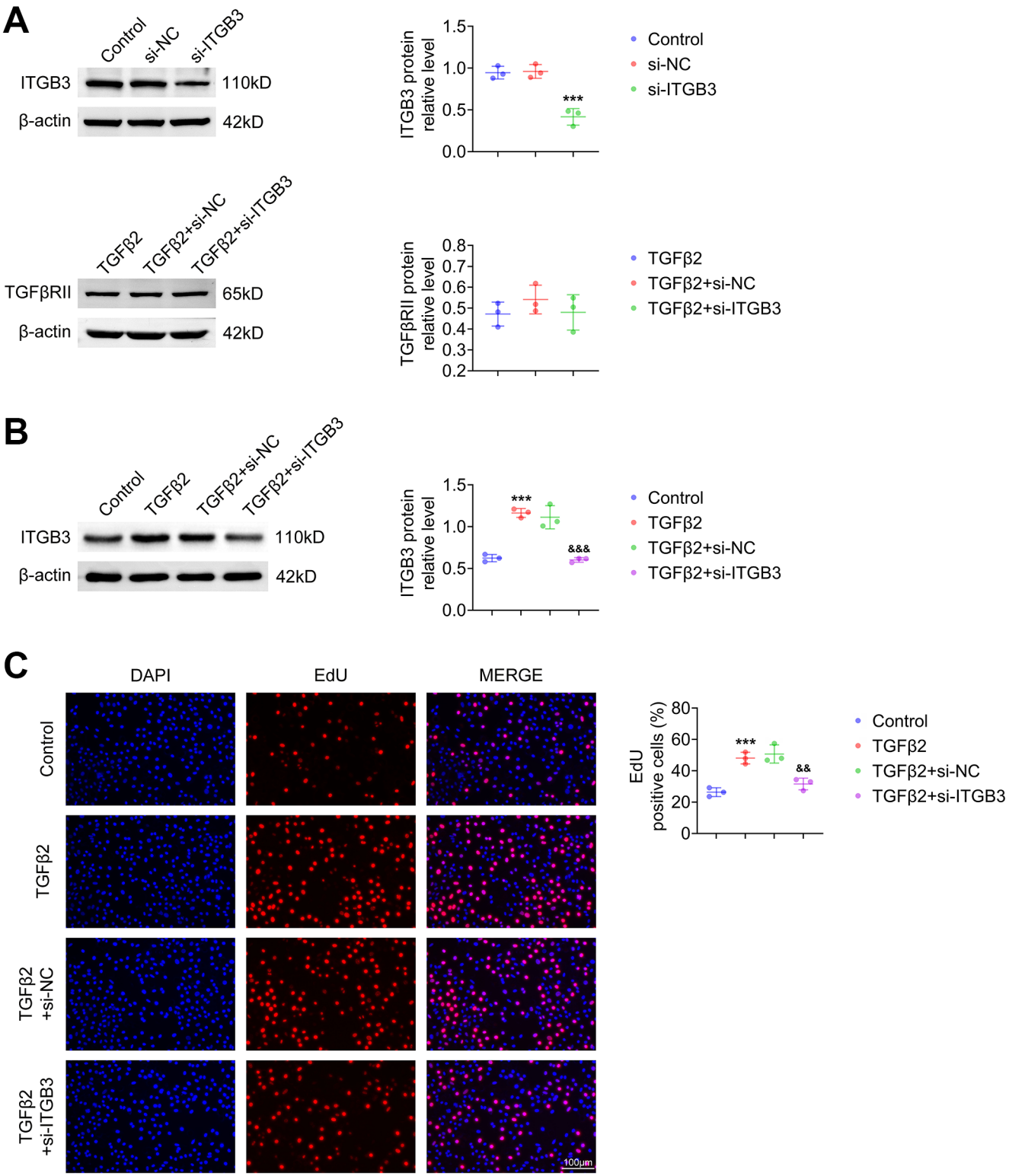

Fig. 2. Inhibition of *ITGB3* attenuates proliferation of transforming growth factor (TGF)-β2-treated HLE-B3 cells. A. Western blot analysis of ITGB3 protein expression in the control, si-NC (negative control), and si-ITGB3 groups; TGFβRII protein expression was assessed in the TGF-β2, TGF-β2 + si-NC, and TGF-β2 + si-*ITGB3* groups; B. Western blot analysis of *ITGB3* protein expression in the control, TGF-β2, TGF-β2 + si-NC, and TGF-β2 + si-*ITGB3* groups; C. Proliferation of HLE-B3 cells in the control, TGF-β2, TGF-β2 + si-NC, and TGF-β2 + si-*ITGB3* groups was evaluated using the 5-ethynyl-2′-deoxyuridine (EdU) assay (n = 3, $^{**}p < 0.01$, $^{***}p < 0.001$)

adhesion, EMT, and migration in PCO.[20] In addition, silibinin has been reported to inhibit TGF-β2-mediated EMT and migration of LECs, thereby reducing PCO progression.[21]

Importantly, *ITGB3* has been shown to enhance EMT in several diseases.[22–24] Consistent with these findings, our study demonstrated that *ITGB3* knockdown reduced the migration of HLE-B3 cells, as shown by transwell and

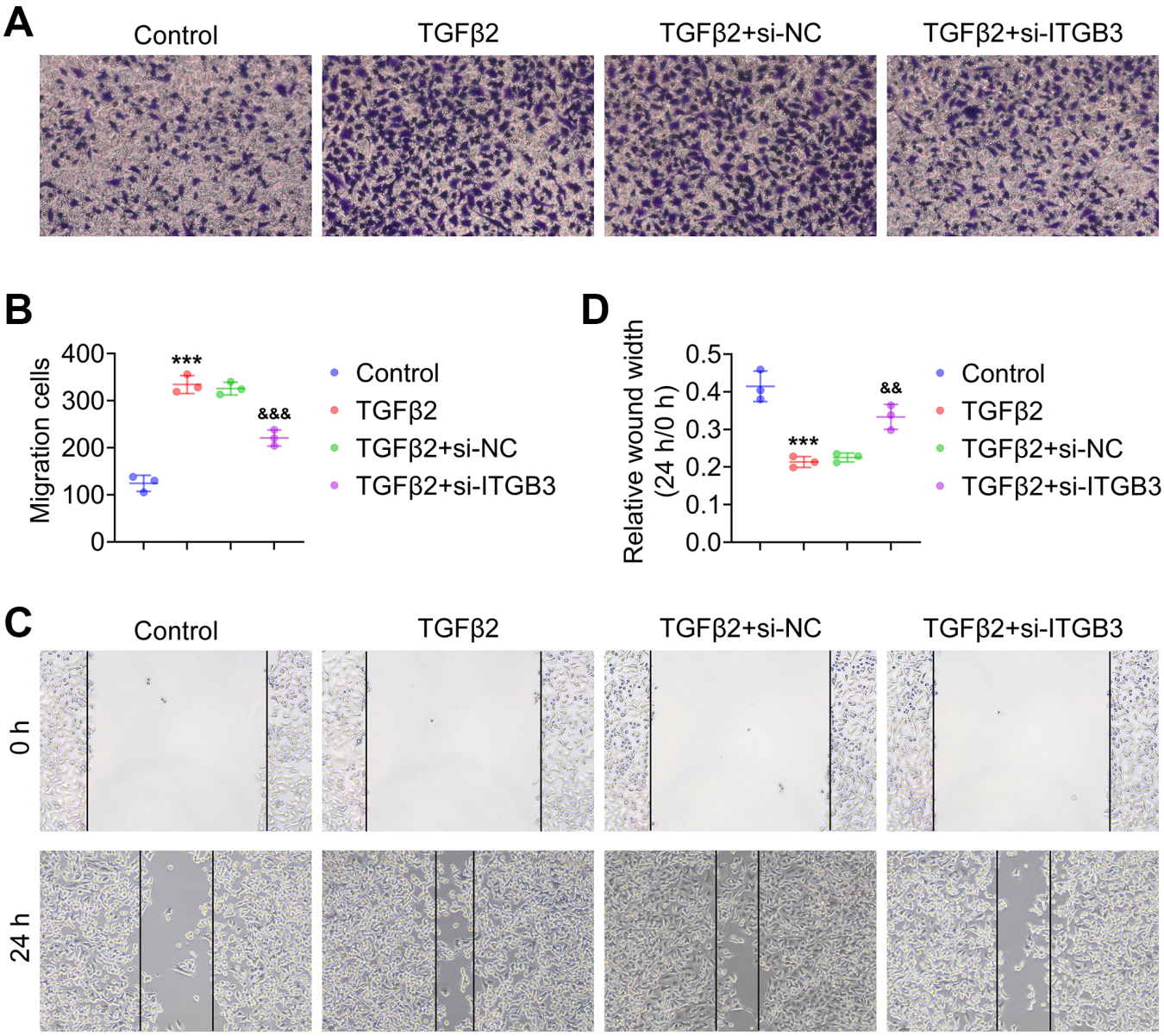

Fig. 3. Knockdown of *ITGB3* suppresses HLE-B3 cell migration. Cell migration was assessed in the control, transforming growth factor (TGF)-β2, TGF-β2 + si-negative control (NC), and TGF-β2 + si-ITGB3 groups using (A,B) the transwell migration assay and (C,D) the wound-healing assay (n = 3, **p < 0.01, ***p < 0.001)

wound-healing assays. Moreover, the EMT process enhanced by TGF-β2 stimulation was effectively reversed following *ITGB3* suppression.

The TGF-β/Smad2/3 signaling pathway plays a pivotal role in the progression of PCO. For instance, metformin has been shown to alleviate EMT in LECs through the AMPK/TGF-β/Smad2/3 pathway,[25] while FGF-2 regulates TGF-β-induced EMT in LECs by modulating the same pathway, thereby affecting the behavior of LECs in PCO.[26] Similarly, capsaicin has been shown to suppress EMT in TGF-β2-stimulated LECs through inhibition of Smad2/3 activation.[27]

Importantly, *ITGB3* has been shown to enhance TGF-β secretion.[10,11] TGF-β binds to its receptors and promotes the activation of downstream Smad proteins, particularly Smad2 and Smad3.[28,29] In this context, our findings revealed that *ITGB3* knockdown attenuated TGF-β2-induced phosphorylation of Smad2 and Smad3, indicating that *ITGB3* is involved in the regulation of the TGF-β/Smad2/3 pathway during PCO progression.

Limitations of the study

This study has several limitations. First, no human PCO tissue samples were included for validation. Second, the absence of in vivo experiments limits the translational value of the findings. Third, clinical investigations and more detailed phenotypic analyses remain necessary to confirm the role of *ITGB3* in the development of PCO. Fourth, although we followed previous studies and applied

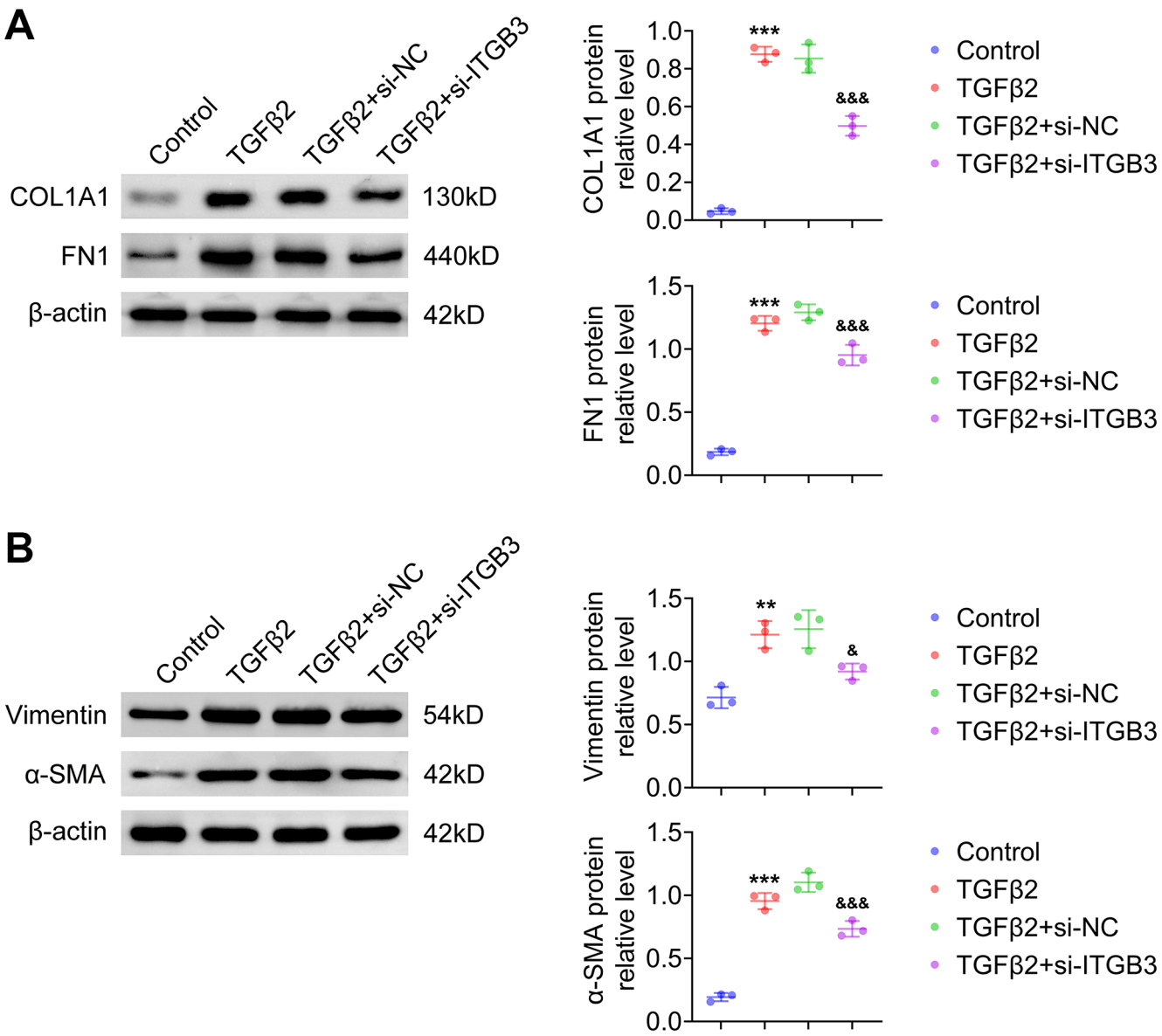

Fig. 4. Suppression of *ITGB3* attenuates epithelial–mesenchymal transition (EMT) progression in HLE-B3 cells. Western blot analysis was performed in the control, transforming growth factor (TGF)-β2, TGF-β2 + si-negative control (NC), and TGF-β2 + si-ITGB3 groups. A. Protein expression of E-cadherin and N-cadherin; B. Protein expression of vimentin and alpha-smooth muscle actin (α-SMA) (n = 3, *p < 0.05, **p < 0.01, ***p < 0.001)

parametric tests (e.g., t-tests), our small sample size may compromise statistical reliability, resulting in variability in p-values, confidence intervals, and sensitivity to outliers, thereby potentially affecting our findings. Therefore, future studies with larger sample sizes are needed for further validation.

Conclusions

This study demonstrated that *ITGB3* knockdown alleviates TGF-β2-induced proliferation, migration, and EMT in HLE-B3 cells. Furthermore, *ITGB3* silencing suppressed activation of the TGF-β/Smad2/3 signaling pathway. These findings support *ITGB3* as a promising molecular target for the prevention and treatment of PCO and may contribute to the development of future translational strategies aimed at improving postoperative outcomes in patients undergoing cataract surgery.

Data Availability Statement

The datasets supporting the findings of the current study are openly available in Zenodo at https://doi.org/10.5281/zenodo.17607776.

Consent for publication of personal information

Not applicable.

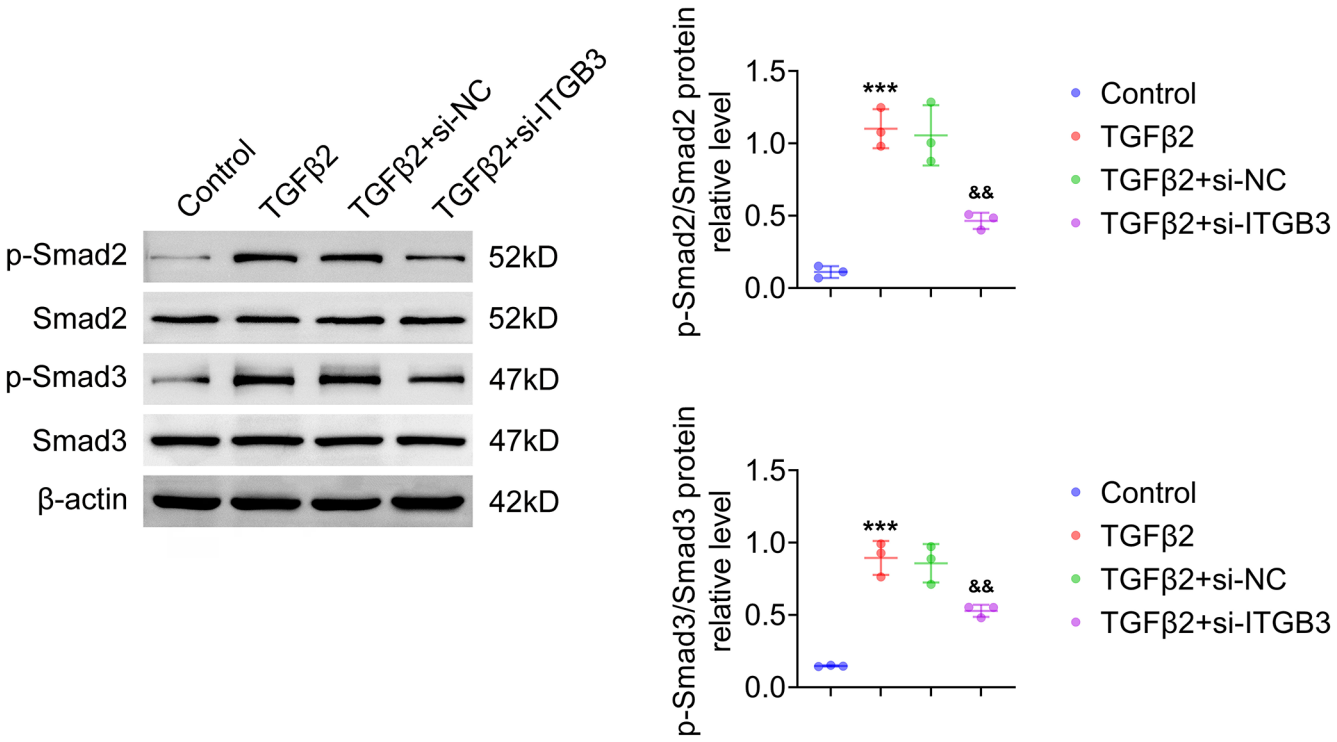

Fig. 5. *ITGB3* knockdown inhibits activation of the transforming growth factor (TGF)-β/Smad2/3 signaling pathway. Protein expression of p-Smad2, Smad2, p-Smad3, and Smad3 was analyzed using western blotting in the control, TGF-β2, TGF-β2 + si-NC (negative control) and TGF-β2 + si-ITGB3 groups (n = 3, *p < 0.05, **p < 0.01, ***p < 0.001)

Use of AI and AI-assisted technologies

Not applicable.

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